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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,840	09/05/2001	Peter Francis Leadlay	0380-P02382U	6757

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DANN DORFMAN HERRELL & SKILLMAN
SUITE 720
1601 MARKET STREET
PHILADELPHIA, PA 19103-2307

EXAMINER
KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,840	LEADLAY ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-40* is/are pending in the application.

4a) Of the above claim(s) *31-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-30 and 38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (Paper No. 7 mailed on February 4, 2002), Applicants filed an election and an amendment (Paper No. 9). Applicants cancelled all previously pending claims and added new claims 17-40.

Election

2. Applicants' election with traverse of Group I (previous claims 1-7, 13, and 16), drawn to PKS-containing systems, in Paper No. 9 is acknowledged. Applicants note on page 16 of their remarks that this Group is drawn to new Claims 17, 20, and 28-30; the Examiner disagrees. New claims drawn to the elected subject matter of Group I are Claims 17-30 and 38-40.

The traversal is on the ground(s) that all the pending claims have unity and should be examined together. Applicants go to great lengths discussing the shortcomings of the IPER, which was noted by the Examiner in the previous restriction requirement as a reason why the claims lack a special technical feature above the art and, therefore, lack unity. Applicants particularly focus on a purported newly-recognized feature of loading domains, that is their ability to decarboxylate the developing polyketide chain. This concept of rendering the claims above the prior art is not found persuasive because the instant claims are drawn to previously taught *products*, which products *inherently* have the feature purported as "novel". Thus, any prior art anticipating or obviating the claimed *products*, with out without description of the decarboxylation function of the loading domain, still reads on the pending claims (see art rejections below).

The requirement is still deemed proper and is therefore made FINAL. Claims 17-40 are pending in the instant application. Claims 31-37 are withdrawn from further consideration as non-elected inventions. Claims 17-30 and 38-40 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for International Application No. PCT/GB99/02044 filed on June 29, 1999 and UK Application No. 9814066.4 filed on June 29, 1998 as requested in the declaration. The Examiner notes that the requirements of national stage entry of the instant application had been completed (note assigned U.S. filing date) within 30 months of the earliest claimed priority date; the related international application includes both a search report and a preliminary examination report with copies of references.

Information Disclosure Statement

4. Applicants filed a "Request for Listing References" on February 12, 2002 wherein said references were cited on the PCT/ISA/210. The Examiner acknowledges consideration of said references. The Examiner notes that Applicants have not filed an information disclosure statement.

No information disclosure statement has been filed with the instant application as of the date mailed of the instant Office action. Applicants are reminded that they have a duty to disclose all information, of which they are aware, relevant to the patentability of the pending claims (see 37 C.F.R. § 1.56 and M.P.E.P. § 2000).

Drawings

5. The drawings are considered informal for the reasons detailed in the attached copy of PTO Form 948. Appropriate correction is required prior to allowance.

Compliance with the Sequence Rules

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

a) In Figures 2A-2D, 20 polypeptide sequences are disclosed without benefit of SEQ ID NOs.

b) In Figures 4A-4C, 5 polypeptide sequences are disclosed without benefit of SEQ ID NOs.

c) In Figure 7, DNA sequences are disclosed without benefit of SEQ ID NOs.

d) On the following pages, 2 DNA oligomers are disclosed without benefit of SEQ ID NOs:

page 32, lines 14-15
page 33, lines 19-21
page 43, lines 25-26
page 47, lines 18-19
page 49, lines 17-18
page 53, lines 19-20
page 58, lines 21-22
page 59, lines 10-11
page 63, lines 16-17
page 64, lines 22-23
page 70, lines 16-17
page 72, lines 1-2
page 72, lines 6-7
page 72, lines 13-14

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Objections to the Specification

7. The title is objected to for not adequately describing the claimed subject matter. The Examiner suggests the following new title:

---Hybrid Polyketide Synthases and Novel Loading Domains---

8. The Abstract is objected to for containing an abbreviation, "CLF", without definition. It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential.

9. The specification is objected to for the following informalities:

a) On page 29, the brief description of the drawings is not titled as such.

b) On pages 29 and 30, reference to multiple-sheet figures (Figures 2A, 2B, 2C, and 2D, for example) must be explicit. The Examiner suggests the inclusion of a description of Figures 2A, 2B, 2C, 2D, 4A, 4B, and 4C.

c) On pages 35, 45, 51, and 56, the chemical structure is struck out in the file copy. It is unclear if these are inadvertent stray marks or if the text is cancelled. The Examiner suggests amending these sections to clearly include the chemical structures.

Appropriate correction is required.

10. The amendment filed April 15, 2002 (Paper No. 9) is objected to under 35 U.S.C. § 132 because it introduces new matter into the disclosure. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Claim 26 and Claim 38.

a) For Claim 26, Applicants cite support on page 27, lines 7-14. The Examiner finds no reference to a hydroxymethylmalonyl AT domain here.

b) For Claim 38, Applicants cite support on page 1, lines 12-19. The Examiner finds no reference to the negative limitation of "not composed of the ... tylosin PKS coupled to the spiramycin PKS...". Moreover, no discussion of tylosin or spiramycin is found on page 1.

Applicants are required to cancel the new matter in the reply to this Office Action or cite other portions (page and line number) of the specification as originally filed that can supply clear support for the above amendment.

Claim Objections

11. Claims 17-30 are objected to because of the following informalities:

a) In Claim 17, line 11, the word "13methyl" requires other punctuation to be clear. The Examiner suggests ---13-methyl---.

b) In Claims 18-30, improper dependencies are found. Clearly, the references to Claim 1 are intended for the first claim, Claim 17. The instant claims will be examined as if the dependencies have been corrected.

c) In Claim 30, the Markush group should be punctuated with commas after each lettered item and between items (c) and (d), an ---or--- should separate the items as well.

Appropriate correction is required.

12. Claim 20 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The limitation of having an arginine in the active site of the acyltransferase (AT) domain does not further limit the subject matter of the parent claim for two reasons. Firstly, the active site is undefined and every AT domain has an arginine somewhere. Secondly, an arginine at about position 110 is virtually ubiquitous in known AT domains.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 17-30 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 17, lines 10-11, the phrase "the target polyketide" is unclear

without proper antecedent basis in the claim. The Examiner suggests this phrase be amended to include ---the polyketide produced by the PKS--- wherein the first occurrence of "polyketide synthase" in Claim 17, line 1, reads ---type I polyketide synthase (PKS)---. Appropriate clarification is required.

14. Claims 17-30 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 17, line 12, the parentheses of "(unsubstituted)" render the claim indefinite. It is unclear to the limitation of "unsubstituted" is a part of the claim or not. Appropriate clarification is required.

15. Claim 18 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The abbreviation "KS" first appears in the claims in Claim 18 where its definition is not made plain. The Examiner suggests the following amendment to Claim 18, line 3: delete "ketosynthase-type" and substitute therefor ---ketosynthase (KS)-type---. Appropriate definition in the claims is required.

16. Claims 19, 39, and 40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The abbreviation "CLF" appears in the claims with definition upon its first appearance, or any appearance. Appropriate definition in the claims is required.

17. Claims 22, 29, 39, and 40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The abbreviations "KSq" and "ATq" appear in the claims with definition upon their first appearance, or any appearance. Appropriate definition in the claims is required.

18. Claim 38 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The abbreviation "PKS" first appears in the claims in Claim 38 where its definition is not made plain. The Examiner suggested an amendment above to Claim 17 where the definition of PKS is first written in the claims. Appropriate definition in the claims is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 26 and 38 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

a) For Claim 26, Applicants cite support on page 27, lines 7-14. The Examiner finds no reference to a hydroxymethylmalonyl AT domain here.

b) For Claim 38, Applicants cite support on page 1, lines 12-19. The Examiner finds no reference to the negative limitation of "not composed of the ... tylosin PKS coupled to the spiramycin PKS.. ". Moreover, no discussion of tylosin or spiramycin is found on page 1.

Applicant is required to cancel the new matter in the reply to this Office Action or cite other portions (page and line number) of the specification as originally filed that can supply clear support for the above amendment.

20. Claims 17-30 and 38-40 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 17, 38, and 39 are drawn to a type I polyketide synthase claimed with function and *very limited* structure, dependent Claims 18-22, 28, and 40 nominally further limit the structure of the claimed synthase, dependent Claims 23-26, 30 further limit the function, and dependent Claims 27 and 29 further limit a portion (either loading or extension) of the claimed synthase

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed.

Cir. 1993) (bracketed material in original). To fully describe a genus of protein (enzyme), which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The instant specification describes several species of the claimed genus in the examples – specifically, PKS enzymes having monesin, tylosin, oleandomycin, and spiramycin loading modules and DEBS extender modules. While these examples are numerous, the specification must also identify the common characteristics of the claimed molecules (i.e., structure and function). Figure 4 gives an alignment of 5 type I loading domains but offers no generalized structure/function description. Without such structural/functional descriptions of the genus of claimed molecules, the specification lacks adequate description of the claimed genus.

21. Claims 17-30 and 38-40 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for polyketide synthases (PKSs) that are combinations of known, defined modules, does not reasonably provide enablement for PKSs of unknown, undefined modules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To enable the claimed genus would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The specification provides no guidance or working examples in the identification of PKSs, their encoding genes, the division of their modules, etc. At the time of the invention, the state of the prior art was limited in its description of modular, type I polyketide synthase enzymes and their sources. The predictability of new PKSs, their sources and their structures, is very low. Thus, one of skill in the art would be required to perform undue experimentation of make the full scope of the claimed invention.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. Claims 17, 18, 20-22, 24, 28, 29 and 30 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kuhstoss *et al.* (Production of a novel polyketide through the construction of a hybrid polyketide synthase. Gene (1996) 183:231-236). The instant claims are drawn to a polyketide synthase (PKS) that is a hybrid of a loading module and extension modules from different sources.

Kuhstoss *et al.* teach a hybrid polyketide synthase (PKS) comprised of the loading module (KS^Q-AT-ACP) of the tylosin PKS and the extension modules of spiramycin PKS (see page 233, left column and Figure 3). The loading module of the tylosin PKS **inherently** has the capacity for decarboxylation as itemized in Claim 17. Said tylosin loading and spiramycin extension modules are not naturally associated with each other. The hybrid PKS produces a 16-membered polyketide (see Figure 3), which production attests to the ability of the loading domain to supply the extension modules with the growing polyketide chain. The loading module of the tylosin PKS contains a KS^Q domain (a ketosynthase domain having a glutamine, not a cysteine, as an active site residue) and the AT domain contains an arginine. The loading module of the tylosin PKS is specific for methylmalonyl-CoA and propionate and includes and acyl carrier protein.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

23. Claims 19, 23, 25, and 38-40 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Khosla (Harnessing the Biosynthetic Potential of Modular Polyketide Synthases. Chemical Reviews (1997) 97:2577-2590). The instant claims are drawn to hybrid PKS enzymes and loading domains using loading domains containing CLF, $AT_{malonyl}$, and $AT_{ethylmalonyl}$ domains.

Khosla *et al.* teach the basic construction of type I and type II PKS enzymes. For type I, the enzymes minimally contain a ketosynthase (KS) domain, an acyltransferase (AT) domain, and an acyl carrier protein (ACP) domain (see column 19, lines 12-20). For type II, the enzymes contain a KS and AT gene, a chain length factor (CLF) gene, and an ACP gene (see column 2, lines 23-30). Khosla *et al.* teach hybrid PKS enzymes using a combination of "enzymes, modules, active sites or portions thereof derived from aromatic, modular or fungal PKS gene clusters" (see column 10, lines 40-45). Thus, Khosla *et al.* teach the combination of any of these domains to produce a minimal PKS. Khosla *et al.* specifically teach hybrid PKS enzymes combining type I and type II genes (see column 9, lines 47-50), which would include a loading domain containing a CLF domain in a PKS enzyme. Khosla *et al.* specifically teach optional polyketide gene clusters such as spiramycin (see column 14, line 31), whose AT domains use

malonyl-CoA and ethylmalonyl (see Khosla page 2581, left column). Khosla *et al.* teach no differentiation between loading module AT domains and other AT domains, thus mixing and matching of all domains is wholly described.

It would have been obvious to one of ordinary skill in the art to use the teachings of Khosla *et al.* to produce the claimed inventions because Khosla *et al.* describe all possible combinations of genes, modules, domains, and portions thereof. One would have been motivated to produce such PKS enzymes because of the great therapeutic potential of novel polyketides that can be easily produced, in combinatorial fashion, using the system of mixing and matching described by Khosla *et al.* One would have had a reasonable expectation of success that such combination of genes, modules, domains, and portions thereof would render functional polyketides due to the extensive similarities among modular and aromatic PKS enzymes (see Khosla).

Other Art of Relevance

24. Marsden *et al.* (Engineering Broader Specificity into an Antibiotic-Producing Polyketide Synthase. Science (Jan, 1998) 279:199-202) teach the combination of the loading module of the avermectin PKS and the extension modules of the erythromycin PKS. The hybrid PKS of Marsden *et al.* produces a 14-membered macrolide, such as in the "proviso" statement in Claim 17. Therefore, Marsden *et al.* cannot be used as art against Claims 17-30 and 38.

Conclusion

25. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
May 1, 2002